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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/211,800 06/22/94 EKINS

PATENTEE

R 6174

EXAMINER

REES, P

ART UNIT

PAPER NUMBER

DANN, DORFMAN, HERRELL AND SKILLMAN
 1601 MARKET STREET
 SUITE 720
 PHILADELPHIA, PA 19103-2307

18N2/0620

1807

DATE MAILED:

06/20/95

This is a communication from the examiner in charge of your application.
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FEB 07 2007

This application has been examined Responsive to communication filed on _____ This action is made final. OPLA

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
 Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892.
2. Notice of Draftsman's Patent Drawing Review, PTO-948.
3. Notice of Art Cited by Applicant, PTO-1449.
4. Notice of Informal Patent Application, PTO-152.
5. Information on How to Effect Drawing Changes, PTO-1474.
6.

Part II SUMMARY OF ACTION

1. Claims 1-31 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. Claims _____ have been cancelled.

3. Claims _____ are allowed.

4. Claims 1-31 are rejected.

5. Claims _____ are objected to.

6. Claims _____ are subject to restriction or election requirement.

7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable; not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been approved by the examiner; disapproved by the examiner (see explanation).

11. The proposed drawing correction, filed _____, has been approved; disapproved (see explanation).

12. Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.

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Part III DETAILED ACTION

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Specification

1. This application does not contain an Abstract of the Disclosure as required by 37 C.F.R. § 1.72(b). An Abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

2. Claims 1-18, and 26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

- a) Claims 1,3-18, and 26 are rejected over the use of the phrases "a small amount" and an "insignificant effect on the concentration of the analyte" as it is not clear how a "small amount" is defined and therefore what an "insignificant effect" is. The claims might be amended by defining the binding capacity of the capture binding agent (as was done in claim 2 for example).

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b) Claims 1,2,4,6,7-18, and 26 are rendered further vague and indefinite over the use of the phrases "immobilized at high density" as it is not clear how "high density" is defined and therefore it is not clear what the metes and bounds of the claims are. The claims might be amended by defining a range of densities

c) Claim 4 is further rejected over the use of the phrase "one or more microspots" as it is not clear what the upper range of microspots is to be. The claim might be amended by defining this range.

d) Claim 8 is further rejected over the use of the phrase "provided on their surface with negatively charged or positively charged groups" as it is not clear where the charged groups are on the microsphere and under what conditions, for example, pH, the group has a charge. The claim might be amended by deleting "are provided" and substituting --having on their surface-- and defining the pH conditions used.

e) Claim 10 is further rejected over the use of the phrase "colour range compatible with a standard filter set" as it is not clear how a "standard filter set" is defined and therefore what the color range is. The claim might be amended by defining the color range.

f) Claims 11 and 26 are further rejected over the use of the phrase "signal strength capable of being determined" as it is not clear under what conditions the signal is capable of being

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determined by time-resolved fluorescence techniques. The claim might be amended by omitting the words "capable of".

g) Claim 17 is further rejected over "twin-stranded DNA sequences" and over the phrase "recognises another part of the corresponding DNA sequence" and "recognises residual single-stranded". The phrases "twin-stranded DNA" and "recognizes", in this context, lacks scientific meaning. The claims might be amended by replacing "twin-stranded" with --double-stranded-- and replacing "recognizes" with --hybridizes to--.

3. Claims 19-21, and 27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

a) The phrases "capable of recognizing analyte in the liquid sample" and "capable of recognizing and binding with either another part of the analyte or the residual probe" render the claims vague and indefinite because it is not clear under what conditions the DNA probe is to bind (for example, at room temperature and low salt conditions, all DNA sequences will bind to each other), and further the term "recognises" in this context

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lacks scientific meaning. The claims might be amended by omitting the words "capable of" and "recognises" and substituting --hybridizing to an analyte under conditions of high stringency-- and --hybridizing with either another part of the analyte or the residual probe--

b) The phrases "small amount" and insignificant effect" render the claims unclear as stated in paragraph 2a.

c) The phrase "immobilized at high density" renders the claim unclear as described in paragraph 2b.

4. Claims 22-25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

a) The phrase "capable of binding" renders the claims unclear as described in paragraph 3a.

b) The phrase "small amount" and insignificant effect" renders the claims (22 and 23-25) unclear as described in paragraph 2a.

c) The phrase "immobilized at high density" renders the claims unclear as describe in paragraph 2b.

5. Claims 29-31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point

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out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

- a) The phrases "small amount" and "insignificant effect" renders the claims vague and indefinite as described in paragraph 3a.
- b) The phrase "one or more microspots" renders the claims vague and indefinite as it is not clear what the upper range of microspots is to be.
- c) Claim 31 is further rejected over the use of the phrase "capable of binding to" which renders the claim vague and indefinite as described in paragraph 3a.

6. Claim 1 is rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 706.03(f).

Claim 1 fails to recites a step that states that the object of the method as recited in the preamble of the claim is accomplished, i.e. no step is actually recited which states how a comparison with a dose-response curve computed from standard samples is to be performed.

7. Claim 19 is rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps, such

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omission amounting to a gap between the steps. See MPEP § 706.03(f).

Claim 19 fails to recite a step that states that the object of the method as recited in the preamble of the claim is accomplished, i.e. no detection step is recited.

8. Claim 26 is rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 26 adds no further limitations to the process of claim 11.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 7, 8, 12, 17-21, and 27, drawn to a method of measuring a concentration of an analyte in a liquid sample

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wherein a capture binding agent immobilized at high density on a solid support, having binding sites specific for the analyte and a developing binding material, which binds to an insignificant fraction of analyte, is used and wherein microspheres which are less than 5 um and carrying a marker are used as a label whose signal strength is representative of the fractional occupancy of the binding sites on the capture binding agent, and further wherein the developing binding material may be an oligonucleotide, are rejected under 35 U.S.C. § 102(e) as being anticipated by Cheung (USPAT 5132242, filed Nov 13, 1989).

Cheung teaches a method of using avidin/Fluorescent microspheres to detect gene sequences (a noncompetitive assay) wherein capture binding agents (in this example, chromosomes) are immobilized on a solid support (i.e glass slides) (column 9, lines 44-60) and wherein developing binding materials used are biotin-labelled DNA probes (see abstract, line 10) and further where in labels bind to the developing binding material which are microspheres, less than 500 Angstroms in diameter (i.e less than 5 um, and further, between 0.01 to 0.5 um) (column 4, line 43), composed of latex (column 3, line 40), and which have charged groups on their surfaces at certain pHs (see Figure 1), wherein the fluorescent microsphere produces a signal whose strength is representative of the fractional occupancy of the binding sites on the capture binding agent (i.e "fluorescent microspheres are attached consistently to the

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location of a specific chromosome" (column 10, lines 1-3). The fluorescent signal is detected by fluorescent microscopy using A filter (a filter for examining dansyl fluorescence) (column 10, lines 2-7).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

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Claims 1-6, 7, and 11-31, drawn to a binding assay method as described in paragraph 9, to kits useful in performing said method, and to a method for performing a plurality of assays, using universal marker reagents, are rejected under 35 U.S.C. § 103 as being unpatentable over Ekins (USPAT 5171695, filing date Feb 3, 1989) in view of Cheung (USPAT 5132242, filed Nov 13, 1989). Ekins teaches a method of measuring the concentration of an analyte in a solution (the sample size which may be 1ml (column 11, line 40), in competitive or noncompetitive assays (column 1, line 45, and column 10, lines 65-70) using a receptor molecule, which may be an antibody, (column 7, lines 25-30)) with binding sites for an analyte (i.e a capture binding molecule) where "the sample is contacted with such a small amount of the receptor, having regard to the affinity of the analyte, that only an insignificant fraction of the analyte becomes bound to the receptor (where less than 5% of the analyte is bound (column 10, lines 30-35)). The receptor having fractionally occupied binding sites is then back titrated by means of a back titration technique involving a system including a second marker different from the first (i.e a developing binding agent, which may also be an antibody (column 7, lines 44-50), and the relative strengths of the two signals produced by the two markers are measured to provide a value representative of the fractional occupancy of the binding sites on the receptor molecule (the capture binding agent) by the analyte. The values are compared with one or more

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corresponding values obtained in the same way using one or more standard liquid samples of known analyte concentration."

(Abstract, parentheses are the examiner's). Ekins teaches that capture binding agent may be immobilized on a solid support at high density (and that the capture binding agent may also be attached to microbeads which are in turn immobilized), that the microspots may have an area of 1mm² or less (column 9, line 36), and that a plurality of capture binding agents may be so immobilized for the purpose of simultaneously conducting multiple analyte detection assays simultaneously (column 9, lines 3-27, and lines 65-68). Ekins also teaches the detection of fluorescent signals using a time-resolved fluorescence technique. (column 10, lines 24-30) and the compositions used in the method may be packaged in a kit for commercial use (column 11, lines 5-9). Ekins does not teach that the label may be fluorescent microspheres.

However Cheung teaches the use of avidin/fluorescent microspheres to detect the binding of developing binding agents (which are labeled with biotin) to capture binding agents immobilized on solid supports (chromosomes bound to glass slides) (see paragraph 5). Cheung also teaches that the binding of microspheres may be blocked by a noninterfering protein, such as polylysine, to prevent nonspecific binding interactions in hybridization reactions (column 9, line 35). Therefore it would have been prima facie obvious to one of ordinary skill in the art

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at the time the invention was made to use fluorescent microspheres as a label in the method of Ekin, the motivation to do so being provided by Cheung, that "a single fluorescent microsphere is detected by fluorescent microscopy (abstract, lines 7-12) and to "increase the sensitivity and resolution of substrates which heretofore were not detectable, such as precise resolution of antigenic sites and rapid high resolution mapping of single gene sequences" (column 3, lines 10-15).

11. Claims 8 and 9, drawn to a binding assay method where the microspheres contain negatively or positively charged groups on their surface and fluorescent labels within them ,are rejected under 35 U.S.C. § 103 as being unpatentable over Ekins (USPAT 5171695, filed Feb 3, 1989) in view of Cheung (USPAT 5132242, filed Nov 13, 1989) and further in view of Mandle et al. (USPAT 4372745, Feb. 8, 1983). Ekins and Cheung meet all of the limitations of the claim as described in paragraph 10 except for the use of fluorescent labels provided within microspheres and surface charges on the microspheres.

However, Mandle teaches microencapsulated fluorescers which may possess positive, negative or neutral charges on their surface (column 19, lines 1-2), and a method of detecting analytes in solution using said fluorescers conjugated to an antibody, as well as kits to detect biological analytes

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comprising said microencapsulated fluorescers (column 4, lines 15-20). Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Ekins using fluorescent labeled microspheres of Mandle as a variant of the microspheres described by Cheung, the motivation to do so being provided by Mandle to "provide a novel class of conjugated microencapsulated fluorescer/biological compositions useful in the detection of various biological analytes of interest." (column 4, lines 13-16).

12. Claim 10, drawn to a binding assay method as described in paragraph 9, 10 and 11, and further where the fluorescent label is an oil-soluble dye, is rejected under 35 U.S.C. § 103 as being unpatentable over Ekins (USPAT 5171695, filed Feb 3, 1989) in view of Cheung (USPAT 5132242, filed Nov. 13, 1989) and further in view of Mandle et al. (USPAT 4372745, Feb. 8, 1983) and Wagner et al. (USPAT 4978625, Dec 18, 1990). Ekins in view of Cheung and further in view of Mandle meet all of the limitations of the claim as described in paragraph 10 and 11 except for the of an oil-soluble fluorescent dye. However Wagner et al. teaches the use of oil soluble fluorescent dyes as labels in methods to detect analytes (column 3, lines 35-40). Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to perform the method of Ekins using fluorescent microspheres using

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oil soluble fluorescent dyes, the motivation to do so provided by Wagner to provide dyes which will not leak out of a microsphere, for example in the form of a lipid bilayer, and to be able to detect a fluorescent signal without rupturing the microsphere (column 3, lines 35-50).

13. The following references, though not relied upon, are cited to demonstrate the state of the prior art:

Soini (USPAT 5028545, Jul 2, 1991) teaches a bispecific multianalyte assay method which uses fluorescent microspheres to be used to detect a plurality of analytes (column 2, lines 38-68, column 3, lines 1-36).

Stuart et al (USPAT 4732847, Mar 22, 1988) teaches antibodies specific to double-stranded DNA (see abstract).

14. No claims are allowed.

15. Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989).

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An inquiry regarding this communication should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1156.

Calls of a general nature may be directed to the Group receptionist who may be reached at (703) 308-0196.

W.G.J.
W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800

6/12/95

Dianne Rees
Dianne Rees

June 6, 1995